Utility of the Nonabsorbed (<0.4%) Antibiotic Rifaximin in Gastroenterology and Hepatology

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Abstract: Oral antibiotics have probable or documented therapeutic utility for multiple enteric conditions commonly treated by gastroenterologists and hepatologists, but they are not frequently prescribed. Barriers to antibiotic use include concerns about bacterial resistance, drug interactions, and antibiotic-associated side effects and toxicity, particularly in vulnerable populations. The use of minimally absorbed oral antibiotics has been suggested as an approach to overcoming some of these barriers, but minimally absorbed antibiotics have not been an important part of the US gastroenterologists' or hepatologists' armamentarium until recently. The 2004 introduction in the United States of the nonabsorbed (<0.4%) oral antibiotic rifaximin is cause for reassessing the potential usefulness of minimally absorbed oral antibiotics for bacterial enteric illness. Rifaximin has broad-spectrum in vitro antibacterial activity against enteric pathogens, gut-localized action, and minimal systemic absorption—a profile consistent with usefulness for a range of enteric conditions involving a pathogenetic role of bacteria. The emerging clinical profile of rifaximin also supports its potential utility for multiple enteric conditions. Rifaximin has a tolerability profile comparable to that of placebo and is not known to interact clinically with other medications. The efficacy of rifaximin is well documented for the treatment of infectious diarrhea caused by noninvasive pathogens and hepatic encephalopathy. A growing body of data supports the efficacy of rifaximin for additional enteric conditions, such as Crohn's disease, ulcerative colitis, small-intestinal bacterial overgrowth, pouchitis, and antibiotic-associated colitis, that are characterized by acute bacterial infection or bacterial colonization. In addition, rifaximin has recently been demonstrated effective in the prevention of travelers' diarrhea and shigellosis in controlled clinical studies. Ongoing studies and more experience with rifaximin in clinical practice will help to further define the role of this antibiotic in gastroenterology and hepatology.

Keywords
Rifaximin, antibiotic, minimally absorbed.

Oral antibiotics have probable or documented therapeutic utility for multiple enteric conditions commonly treated by gastroenterologists and hepatologists. The clinical benefits of antibiotics in acute bacterial diarrheal illness, small-intestinal bacterial overgrowth (SIBO), and *Helicobacter pylori*–associated peptic ulcer disease have been demonstrated in controlled studies,[1-3] and data suggest a potentially important role of antibiotics as primary or adjunctive therapy in conditions such as hepatic encephalopathy, Crohn's disease, and irritable bowel syndrome (IBS).[4-6] Their potential applications for enteric conditions notwithstanding, oral antibiotics are infrequently prescribed in ambulatory care in gastroenterology and hepatology.[7] Barriers to antibiotic use include concerns about the potential for contributing to bacterial resistance, drug interactions, and antibiotic-associated side effects and toxicity, particularly in vulnerable populations.[8-12]

The use of minimally absorbed oral antibiotics has been suggested as an approach to overcoming some of these barriers.[12-14] Limited intestinal absorption permits attainment of high intraluminal drug concentrations for targeting antibacterial activity directly to the enteric site of action while avoiding exposure of other body systems. Because the minimally absorbed oral antibiotic is not available in the bloodstream, body systems other than the gut are not exposed to it, and the risk of systemic toxicity, side effects, and drug interactions is correspondingly low. Theoretically, minimally absorbed oral antibiotics are also less likely than systemically available antibiotics to be associated with widespread bacterial resistance. Because minimally absorbed oral antibiotics are not useful for nonenteric infections, their use is limited relative to that of systemically available antibiotics, which are often used for infections affecting any of several body systems. Circumscribed use arguably limits the selective pressure for the development of bacterial resistance relative to the greater pressure occurring with the widespread and/or frequent use of a systemic antibiotic.

Minimally absorbed antibiotics have been studied in bacterial enteric illnesses but have not generally been an important part of the US gastroenterologists' or hepatologists' armamentarium. Shortcomings that have limited the use of some minimally absorbed antibiotics for enteric conditions include narrow or no coverage of enteropathogens (eg, paromomycin), bacterial resistance (eg, vancomycin), bioavailability sufficient to cause systemic toxicity despite being minimally absorbed (eg, neomycin), and lack of availability in oral form for human use (eg, aztreonam [Azactam, Bristol-Myers Squibb], bicozamycin).

The 2004 introduction in the United States of the nonabsorbed (<0.4%) oral antibiotic rifaximin (Xifaxin, Salix) is cause for reassessing the potential utility of minimally absorbed oral antibiotics for the treatment of bacterial enteric illness. Rifaximin is indicated in the United States for the treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli*, has been granted orphan drug status for the treatment of hepatic encephalopathy, and is under study for potential additional indications. The drug was first marketed in Italy in 1987 and is now approved in 19 countries. Indications have varied by country, but include treatment of bacterial illnesses such as infectious diarrhea and hepatic encephalopathy and for pre- and postsurgical prophylaxis of gastrointestinal infections. It has also been studied and used for prevention of infectious diarrhea as well as the treatment of intestinal bacterial overgrowth, *Clostridium difficile*–associated colitis, diverticular disease, Crohn's disease, pouchitis, peptic ulcer disease, and IBS. This article reviews preclinical and clinical data on rifaximin and considers its place in the management of enteric conditions.

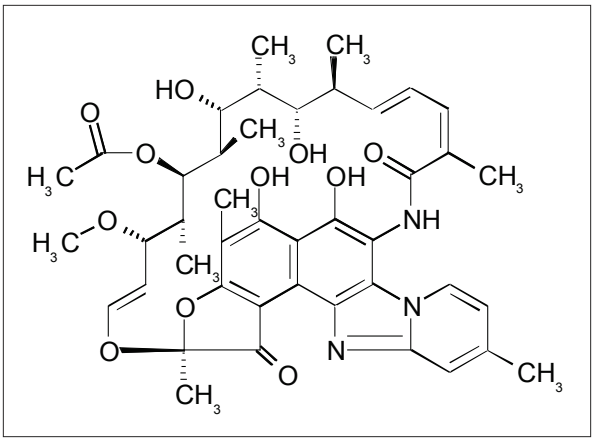

Figure 1. The chemical structure of rifaximin.

Rifaximin Chemical Structure

Rifaximin (Figure 1) is a nonsystemic antibiotic modified from its parent compound, rifamycin, to achieve low absorption and potent antimicrobial activity.[15] Rifaximin is a structural analog of the rifamycin rifampin[16] but differs from rifampin in containing a pyridoimidazole system that confers unique pharmacologic properties such as minimal absorption.[15]

Antibacterial Activity

Bacterial susceptibility to antibiotics is typically assessed by measuring the minimum inhibitory concentration (MIC), which is defined as the lowest concentration of the antibiotic that prevents visible bacterial growth after 18 or 24 hours of incubation in dilution tests.[17] MIC breakpoints have typically been established based on

several factors, including the concentration of drug in the plasma. Because rifaximin is essentially not absorbed, establishing MIC breakpoints by taking into consideration plasma concentrations is not useful. Because the clinically relevant concentration of rifaximin is that in the feces rather than the plasma, rifaximin fecal levels are typically measured to help determine bacterial susceptibility. Across studies, the highest MICs with rifaximin for a range of enteropathogens, including *H. pylori* and *C. difficile*, were orders of magnitude lower than the fecal concentration of rifaximin (4,000–8,000 µg/mL) during clinical use (Table 1).[18,19] The results demonstrate potent and broad-spectrum in vitro activity of rifaximin.

Whether the broad-spectrum in vitro antibacterial activity of rifaximin corresponds to in vivo microbiologic eradication is currently being investigated. Rifaximin was effective at eradicating causative pathogens in studies of travelers' diarrhea that enrolled patients infected with *E. coli* and other diarrheal pathogens.[20,21] The efficacy of rifaximin at eradicating invasive pathogens has not been well established to date and warrants additional elucidation. Additional investigations to further define the in vivo bacteriologic activity of rifaximin are under way.

Clinical Pharmacokinetics

Oral Bioavailability

Pharmacokinetic studies show that rifaximin is virtually not absorbed from the gastrointestinal tract in healthy volunteers. The pharmacokinetics of radiolabeled rifaximin (^{14}C-rifaximin) administered as a single oral dose (400 mg) to four healthy men aged 30–41 years were assessed via radioactivity measurement for the 168 hours after dosing and via validated liquid chromatography/tandem mass spectrometry assay of plasma and urine samples.[22] No radioactivity was measurable in blood, and rifaximin concentrations were undetectable in most plasma samples. Mean plasma concentrations of rifaximin ranging from 13.0 to 20.6 ng-eq/mL were detected from 0.5 hours to 4 hours after dosing. Mean (± standard deviation) maximum plasma concentration was 4.3 (±2.8) ng/mL, and area under the concentration-versus-time curve through 168 hours postdose was 21.7 (±17.8) ng·hr/mL. Ninety-seven percent of the radiolabeled rifaximin dose was recovered unchanged from the feces, and 0.32% of the dose was recovered from the urine.

A similar pattern of results was obtained in an open-label study of 18 healthy volunteers (mean age, 24 years) who received a single oral dose of rifaximin (400 mg) after a 9-hour fast.[23] Rifaximin was not detectable in plasma samples obtained through 48 hours postdose (lower limit of detection, 2 ng/mL) from 9 of the subjects and was only minimally present (at concentrations ranging from 2 to 5.3 ng/mL) in the remaining 9 subjects. For 14 of 18 subjects, less than 0.01% of the drug was detected as unchanged drug in urine through the 48-hour postdose period.

Results comparable to these findings in healthy volunteers were obtained in studies of patients with gastrointestinal illnesses including ulcerative colitis, Crohn's disease, and shigellosis.[22,24,25] For example, rifaximin plasma concentrations were consistently low during repeated administration (200 mg three times daily for 3 days) to 13 patients with shigellosis.[26] Peak plasma concentrations of rifaximin ranged from 0.81 to 3.4 ng/mL after three doses (day 1) and from 0.68 to 2.26 ng/mL after nine doses (day 3). These data suggest that rifaximin is virtually unabsorbed in conditions characterized by inflamed intestinal tissue and that the drug does not accumulate during short-term administration.

Drug Interactions

No evidence of drug interactions involving rifaximin has been observed in clinical studies or clinical practice. Although rifaximin induced cytochrome P450 (CYP) 3A4 in hepatocytes in vitro,[26] clinical research demonstrates no presystemic or systemic interaction between rifaximin and the CYP3A4 substrate midazolam.[27] Rifaximin also did not affect the metabolism of an oral contraceptive containing ethinyl estradiol and norgestimate in a clinical study.[28] These findings are consistent with the minimal (<0.4%) absorption of rifaximin.

Efficacy of Rifaximin for Enteric Conditions

The clinical efficacy of rifaximin has been studied for several enteric conditions. Rifaximin has been most extensively studied for travelers' diarrhea and for hepatic encephalopathy. Other uses for which rifaximin has been studied as acute antibiotic therapy include ulcerative colitis, Crohn's disease, pouchitis, SIBO, and antibiotic-associated colitis. Rifaximin has also been investigated as a prophylactic treatment for postsurgical infections, travelers' diarrhea, shigellosis, and relapses of diverticulitis.

Bacterial Diarrhea

The efficacy of rifaximin for travelers' diarrhea has been assessed in four randomized, double-blind, parallel-group, controlled clinical trials in patients with diarrhea contracted during travel to Guatemala, Mexico, Kenya, India, or Jamaica.[20,21,29,30] Three of the four studies have been published; the fourth study, which was recently completed, has not yet been published as a full manuscript. The results show that rifaximin was significantly more effective than placebo and comparable to ciprofloxacin (Cipro,

Table 1. In Vitro Activity of Rifaximin Against Bacterial Isolates[19]

	Number of Isolates	MIC_{50}, mg/mL	MIC_{90}, mg/mL	MIC range, mg/mL
Isolates from Patients With Bacterial Diarrhea				
Aeromonas spp	27	16	128	16 to >256
Campylobacter jejuni	54	12.5	>100	0.78 to >100
Campylobacter spp	35	32	128	0.25 to >256
Enteroaggregative *E. coli*	50	64	128	16 to >256
Enterohemorrhagic *E. coli*	17	64	>256	32 to >256
Enteroinvasive *E. coli*	20	64	128	8 to >256
Enterotoxigenic *E. coli*	153	64	128	8 to 256
Plesiomonas shigelloides	25	64	256	16 to >256
Salmonella spp	53	64	128	8 to >256
Shigella spp	88	64	128	32 to >256
Vibrio spp	25	128	128	8 to 128
Yersinia spp	91	12.5	25	0.2 to 25
***Isolates of* H. pylori**				
 In culture median with pH of 6.0	30 43	4 2	4 8	0.5 to 8 0.5 to 8
In culture median with pH of 7.2	30	1	2	0.25 to 4
Isolates of Anaerobic Bacteria (Primarily from Cirrhotic Patients)				
Bifidobacterium spp	6	0.8	6.2	0.4 to 50
C. difficile	4	0.2	0.8	0.2 to 0.8
C. difficile	93	0.004	128	0.004 to 128
Clostridium spp	26	0.4	50	0.0125 to >100
Propionibacterium spp	10	0.2	12.5	0.025 to 12.5
Isolates of Gram-Positive Cocci				
Staphylococcus aureus	51	0.015	>8	≤0.01 to >8
Staphylococcus epidermidis	20	≤0.015	≤0.015	≤0.015
Staphylococcus haemolyticus	10	≤0.015	≤0.015	≤0.015 to >8
Enterococcus faecalis	21	2	8	0.5 to >8
Enterococcus faecium	11	2	>8	≤0.015 to >8
Enterococcus spp	10	0.25	2	≤0.015 to >4
Streptococcus group A	19	0.12	0.25	≤0.03 to 0.25
Streptococcus group B	20	0.12	0.25	0.06 to 0.25
Streptococcus groups C, F, and G	14	≤0.03	0.06	≤0.03 to 0.5
Streptococcus pneumoniae	30	≤0.03	0.06	≤0.03 to >4

MIC = minimum inhibitory concentration.

Table 2. Clinical Efficacy Data From Controlled Clinical Trials of Rifaximin for Infectious Diarrhea[20,29,30]

	Median TLUS, hours (95% confidence interval)	Clinical Cure,* % patients
Study 1		
Rifaximin 600 mg/day for 3 days (n=125)	32.5 (28.4–43.6)	79.2
Rifaximin 1,200 mg/day for 3 days (n=126)	32.9 (24.8–44.0)	81.0
Placebo for 3 days (n=129)	60.0 (48.4–92.0)	60.5
Study 2†		
Rifaximin 800 mg/day for 3 days (n=93)	25.7 (20.9–38.0)	87.1
Ciprofloxacin 1,000 mg/day for 3 days (n=94)	25.0 (18.5–35.2)	88.3
Study 3†‡		
Rifaximin 600 mg/day for 5 days (n=18)	26.3	88.9
Trimethoprim-sulfamethoxazole 320/1,600 mg/day for 5 days (n=17)	47.0	82.4

* Clinical cure was defined as no unformed stools within a 48-hour period with no fever (with or without other clinical symptoms) or no watery stools and no more than 2 soft stools within a 24-hour period with no fever and no other clinical symptoms except for mild excess gas/flatulence.

† No statistically significant differences between rifaximin and comparator. Study 2 was statistically powered to show noninferiority of rifaximin versus the comparator. Study 3 was not statistically powered to show noninferiority of rifaximin versus the comparator.

‡ Data for rifaximin 400 mg TID and rifaximin 600 mg TID arms are omitted.

TLUS = time to last unformed stool.

Bayer) or trimethoprim-sulfamethoxazole at conferring clinical improvement of diarrhea, including reduction of the median time to last unformed (ie, watery or soft) stool (TLUS; primary endpoint). TLUS is defined as the interval of time from the first dose of medication until passage of the last unformed stool and indicates that wellness has been achieved (see Table 2 for results of published studies).[20,29,30] In the as yet unpublished study, which included both ciprofloxacin and placebo groups,[21] rifaximin and ciprofloxacin appeared to be comparably effective at reducing TLUS in the sample as a whole (TLUS=32 hours with rifaximin, 29 hours with ciprofloxacin, and 66 hours with placebo). Rifaximin was particularly effective in this study for the subgroups of patients with diarrheagenic *E. coli* and among whom no pathogen was identified.[21,31] However, neither rifaximin nor ciprofloxacin was effective for inflammatory pathogens, including *Salmonella* and *Campylobacter*. The findings of the four large controlled clinical studies are supported by data from 12 smaller controlled and open-label studies showing rifaximin to be effective for infectious diarrhea in pediatric and elderly patients and adults.[32-43]

Hepatic Encephalopathy

Hepatic encephalopathy is a metabolic disorder characterized by neurologic and other symptoms attributed to the inability of the failing liver to deactivate toxins—particularly ammonia, which is produced by both aerobic and anaerobic bacterial flora in the gut. A primary goal of therapy for hepatic encephalopathy is to reduce the production and absorption of toxins. Antibiotic therapy, one of several management strategies for hepatic encephalopathy, may improve clinical status by reducing ammonia production by gut bacterial flora. Because the patient with hepatic encephalopathy can be vulnerable to drug-associated side effects and drug interactions, use of a well-tolerated antibiotic with low potential for drug interactions is important.

The US Food and Drug Administration (FDA) has granted rifaximin orphan drug status for the treatment of hepatic encephalopathy, and rifaximin is currently undergoing study for possible introduction for this use in the United States. To date, the efficacy of rifaximin in the treatment of hepatic encephalopathy has been assessed in 20 studies including 14 randomized studies with a comparator medication, four open-label studies not including a comparator medication, one dose-finding study, and one placebo-controlled clinical study.[44-61]

Seven of the comparator studies evaluated rifaximin vis-à-vis lactulose or lactitol, which are nonabsorbable disaccharides and the most widely used treatments for hepatic encephalopathy. In one of the largest of these investigations, rifaximin was compared with lactitol in a randomized, double-blind, double-dummy, parallel-group study in 103 patients with grade 1, 2, or 3 hepatic encephalopathy.[47] Improvement in neurologic, neuropsychiatric, and psychometric parameters and reductions in blood ammonia were observed in both groups by the

end of the treatment period. The overall portal systemic encephalopathy index improved more with rifaximin than with lactitol, a finding attributed to greater improvement in the electroencephalogram and greater reduction in blood ammonia levels with rifaximin. The percentage of patients with clinical resolution/improvement at the end of therapy was 82% for rifaximin versus 80% for lactitol. A similar pattern of results was observed in six other comparisons of rifaximin with lactitol or lactulose.[44,48-50,58,59] Both rifaximin and the disaccharide were associated with reductions in blood ammonia levels and improvements in neurologic signs and symptoms in these studies, but rifaximin was often associated with earlier and/or more robust improvement in efficacy than the disaccharide. Results of a 2004 Cochrane meta-analysis that assessed data from several of these trials demonstrated rifaximin to be significantly more effective than nonabsorbable disaccharides (namely, lactulose and lactitol) in the treatment of hepatic encephalopathy.[62]

In other comparator studies, rifaximin was at least as effective as neomycin and paromomycin at reducing blood ammonia levels and improving neurologic signs and symptoms of hepatic encephalopathy.[44,51,56] In some studies, rifaximin appeared to reduce blood ammonia levels and improve neurologic signs and symptoms earlier and/or more effectively than the comparator medications.

Rifaximin has also been evaluated in one of the few placebo-controlled studies to be conducted for the treatment for hepatic encephalopathy.[60] In this recently completed study that has not yet been published in full, 93 patients with hepatic encephalopathy, intolerant of lactulose or lactitol, with mild to moderate changes in mental status were randomized to receive rifaximin 400 mg three times daily or placebo for 14 days. Rifaximin improved several outcomes versus baseline and was statistically significantly more effective than placebo with respect to improving asterixis. Although results across efficacy measures were uniformly more positive with rifaximin than placebo, rifaximin did not differentiate from placebo on the primary endpoint and several secondary endpoints. Targeting a mildly impaired patient population may have affected the results by contributing to a large placebo effect. Greater than expected improvement in the placebo group may have been attributed to the withdrawal of lactulose/lactitol 24–48 hours before initiation of the study medication. The withdrawal of poorly tolerated lactulose/lactitol shortly before study initiation may have resulted in a clinical response that was reflected as improvement in efficacy measurements from baseline. In addition, one might argue that in mild hepatic encephalopathy, asterixis might be a more appropriate measure of a drug's clinical efficacy than measures of mental status.

Inflammatory Bowel Disease

The multifactorial etiology of inflammatory bowel disease (Crohn's disease, ulcerative colitis) appears to involve a pathogenic role for enteric flora and/or enteropathogens.[63] Among other treatment modalities including 5-aminosalicylates, corticosteroids, and immunosuppressive agents, antibiotics have been studied and prescribed as adjunctive therapy for Crohn's disease and ulcerative colitis.

The efficacy of rifaximin for inflammatory bowel disease has been assessed in eight studies,[24,64-70] one of which was double-blind and placebo-controlled and the remainder of which were of open-label design and did not include a control group. In the placebo-controlled study, 28 patients with moderate to severe ulcerative colitis refractory to corticosteroid treatment were randomly assigned to receive either rifaximin 800 mg daily or placebo as an adjunct to standard corticosteroid therapy for 10 days.[24] The percentage of patients with clinically significant improvement (defined as fewer than three bowel movements daily with no blood and no signs of severe systemic colitis) at the end of the treatment period was 64% in the rifaximin group and 42% in the placebo group (difference not statistically significant). Rifaximin-treated patients showed significant improvements at the end of the treatment period compared with baseline in stool frequency, rectal bleeding, sigmoidoscopic score, and clinical activity, whereas placebo-treated patients showed significant improvements in clinical activity only. ("Clinical activity" was not operationally defined in the publication.)

These data are consistent with the results of an open-label study of 10 patients with left-side ulcerative colitis clinically relapsing during maintenance treatment with mesalamine.[64] Rifaximin 400 mg twice daily was added for up to 4 weeks to mesalamine 2.4 g/day. Clinical remission, defined as a final score of less than 6 on Rachmilewitz's Activity Index, was observed in 7 of the 10 patients during rifaximin treatment. Additional findings supportive of the possible benefit of rifaximin in inflammatory bowel disease were obtained in two open-label, uncontrolled studies in which rifaximin treatment was associated with clinically significant improvement (variably defined as reductions in frequency of bowel movements and improvements in stool characteristics or in endoscopic findings) in patients with ulcerative colitis in remission but with abdominal symptoms (n=12)[65] and in patients with a positive stool culture for pathogenic bacteria and a diagnosis of ulcerative colitis or Crohn's disease refractory to treatment with 5-aminosalicylic acid or corticosteroids (n=12).[66]

Rifaximin has also been assessed in open-label studies including only patients with Crohn's disease. In an open-label study of rifaximin (200 mg three times daily) for the treatment of active Crohn's disease (n=29, 23 of whom

completed a 4-month course of therapy),[67] mean Crohn's Disease Activity Index (CDAI) score was reduced by 43% compared with baseline at the end of 4 months of treatment. Clinical remission, defined as a CDAI score of less than 150, was observed at the end of treatment months 1, 2, 3, and 4 by 41%, 56%, 56%, and 59% of patients, respectively. By the end of the study, 78% of the patients had at least a 70-point improvement in CDAI. In a retrospective chart review, rifaximin 200 mg three times daily (n=10) and 400 mg twice daily (n=20) added to other treatments in patients with mild to moderate Crohn's disease was associated with improvement in clinical outcome assessed (by Present-Korelitz score) in 7 of 16 patients (43%) with ileitis, 4 of 6 patients (67%) with ileocolitis, and 5 of 8 patients (63%) with colitis.[68] Improvement in clinical status was also observed during treatment with rifaximin 400 mg twice daily for 10 days–5 months in an open-label assessment of eight patients with severe Crohn's disease refractory to conventional therapy.[69] Median time to response was 8.9 days. In another uncontrolled investigation, rifaximin did not significantly reduce intestinal protein loss (measured as fecal α1-antitripsin levels) after up to 12 months of treatment in patients with inactive Crohn's disease.[70]

Because of their small sample sizes and—for all studies but one—open-label design, none of these studies in patients with ulcerative colitis or Crohn's disease permit definitive conclusions about the adjunctive efficacy of rifaximin in inflammatory bowel disease. However, the data considered in aggregate are consistent with a possible benefit of rifaximin. Additional studies in patients with inflammatory bowel disease are being conducted in an attempt to extend these findings.

Pouchitis

As bacterial overgrowth is thought to play an important role in pouchitis, pouchitis is typically managed with broad-spectrum antibiotics. The efficacy of rifaximin (2,000 mg/day) in combination with ciprofloxacin (2,000 mg/day) for 15 days was assessed in an open-label study conducted in 18 patients with pouchitis who had previously failed treatment with metronidazole, amoxicillin/clavulanate, or ciprofloxacin.[71,72] The results show that 89% of patients either clinically significantly improved (as defined by a decrease from baseline of at least 3 points on the Pouchitis Disease Activity Index; 10 patients; 56%) or went into remission (33%). In a prospective, open-label study of 10 patients with pouchitis, administration of rifaximin 400 mg twice daily for 14 days was associated with complete remission in 8 patients and a greater than 50% response in a ninth patient.[73] All 10 patients reported reduction in fecal urgency and resolution of abdominal pain. A placebo-controlled study to evaluate the efficacy and tolerability of rifaximin monotherapy in pouchitis is in progress.

Small-Intestinal Bacterial Overgrowth

As SIBO is caused by changes in intestinal motility that result in reduced clearance of bacteria from the intestines, suppression of bacterial overgrowth constitutes a goal of treatment. The efficacy of rifaximin in SIBO was assessed in a double-blind trial including chlortetracycline as a comparator and in three uncontrolled, open-label studies. In the double-blind study, patients with SIBO confirmed by hydrogen breath test received either rifaximin 1,200 mg/day (n=10) or chlortetracycline 1 g/day (n=11) for 7 days.[74] Patients in the rifaximin group, but not in the chlortetracycline group, demonstrated significant reductions in fasting, peak, and total hydrogen excretion and decreases in symptom scores for diarrhea, borborygmi, and lassitude at the end of the treatment period. In two of the open-label studies, each of which involved 12 patients with SIBO confirmed by hydrogen breath test, rifaximin normalized results of the hydrogen breath test and reduced diarrheal symptoms in the majority of patients.[75,76] Similarly, in the third open-label study, which involved 14 patients, administration of rifaximin was associated with complete remission in 12 patients and a greater than 50% response in a thirteenth patient.[77] Considered together, the data support the potential utility of rifaximin for SIBO; however, larger, placebo-controlled studies are needed to substantiate the preliminary findings.

Research suggests that SIBO, which is associated with a constellation of symptoms similar to those of IBS, may underlie some of the gastrointestinal symptoms in patients with IBS. In a recent meta-analysis undertaken to assess links between SIBO and IBS, an abnormal lactulose breath test (reflecting the presence of SIBO) was found in 84% of patients with IBS, and eradication of SIBO improved IBS symptoms by 75%, on average.[78] Given the potential usefulness of rifaximin in SIBO, it may also prove to be useful for IBS. In fact, in a recent randomized, double-blind, placebo-controlled study in which approximately two thirds of enrollees met Rome II criteria for IBS, rifaximin 200 mg daily for 10 days (n=56) significantly reduced abdominal bloating and flatulence relative to placebo (n=54).[79] The clinical effect of rifaximin corresponded with a reduction in lactulose hydrogen breath test values compared with placebo. Rifaximin (600, 800, or 1,200 mg/day for 7 days) was also associated with eradication of SIBO in 90 patients with IBS meeting Rome II criteria in a randomized, dose-finding study.[80] The proportion of patients with eradication of SIBO was significantly higher in the group treated

with rifaximin 1,200 mg/day (60.0%) compared with the groups treated with rifaximin 600 mg/day (16.6%) or 800 mg/day (26.6%).

Antibiotic-Associated Colitis

A complication of antibiotic therapy, antibiotic-associated colitis is nearly always caused by overgrowth of *C. difficile*.[81] Toxins released by *C. difficile* damage the intestinal mucosa and cause symptoms such as watery diarrhea, cramps, and fever. Antibiotics most frequently implicated in antibiotic-associated colitis include clindamycin, lincomycins, cephalosporins, and penicillins. Clinical management, which is directed at restoring the normal balance of colonic flora, entails discontinuing the causative antibiotic and initiating an antibiotic effective against the offending pathogen(s) (typically, *C. difficile*).

In vitro, *Clostridium* species are highly susceptible to rifaximin and in fact are the most susceptible of all bacterial species to the drug. The efficacy of rifaximin for *C. difficile*–associated colitis was assessed in an open-label trial with comparator vancomycin.[82] Patients hospitalized with a diagnosis of *C. difficile*–associated colitis confirmed by stool sample were given rifaximin 600 mg/day (n=10) or vancomycin 1,000 mg/day (n=10) for 10 days. By the end of the treatment period, symptoms of colitis had resolved in 9 of 10 rifaximin-treated patients and 10 of 10 vancomycin-treated patients. *C. difficile*–associated toxins were eliminated from stool samples of the majority of patients in both groups during the treatment period, but elimination of toxins occurred significantly more rapidly among vancomycin-treated patients (4.8 days) than among rifaximin-treated patients (8.1 days). A large, randomized, double-blind study comparing rifaximin with vancomycin for the treatment of *C. difficile*–associated colitis is currently ongoing.

Prophylaxis of Postsurgical Infection

Antibiotics are routinely administered for prophylaxis of infection potentially arising after surgery involving the gut. To achieve adequate coverage of the gamut of aerobic and anaerobic pathogens that can cause postsurgical infection, antibiotics are often administered in combination. In a double-blind study of rifaximin for prophylaxis of surgical infection, adult patients who were to undergo colonic surgery received one of three treatments: oral rifaximin 600 mg daily during the 3 days prior to surgery and intravenous placebo 1 hour before surgery; oral placebo daily during the 3 days prior to surgery and intravenous gentamicin (80 mg) 1 hour before surgery; or oral rifaximin 600 mg daily during the 3 days prior to surgery and intravenous gentamicin 80 mg 1 hour before surgery.[83] The results show no differences between the rifaximin group and the gentamicin group in the frequency of wound or nonwound infections, intra-abdominal abscesses, or anastomotic leaks during the postoperative period. However, patients treated with the combination of rifaximin and gentamicin had a significantly lower incidence of postoperative wound infections than those treated with rifaximin and placebo (7.9% versus 15.4%). To date, all other studies of rifaximin for prophylaxis of postsurgical infection are of open-label design.[84-87]

Other Prophylactic Uses of Rifaximin

Data suggest that rifaximin is useful in the prevention of travelers' diarrhea as well as in the prevention of shigellosis. Rifaximin compared with placebo significantly protected against the occurrence of diarrhea in a double-blind, placebo-controlled study in which US adults (n=210) were randomized within 72 hours of their arrival in Mexico to receive rifaximin or placebo for 2 weeks.[88] Rifaximin compared with placebo also protected against the development of shigellosis in healthy volunteers challenged with *Shigella flexneri*.[89]

Safety and Tolerability of Rifaximin

Adverse Events

The occurrence of adverse events, defined as any untoward medical occurrences regardless of suspected cause, was systematically assessed in placebo-controlled clinical trials of rifaximin for travelers' diarrhea. The adverse-event profile of rifaximin did not differ from that of placebo in two randomized, double-blind, placebo-controlled clinical trials in which 320 patients received rifaximin 600 mg daily and 228 patients received placebo for 3 days.[21,26,29] All of the most common adverse events reported with either rifaximin or placebo (eg, flatulence, abdominal pain) are common symptoms of travelers' diarrhea and were unlikely to have been caused by the study medication (Table 3).[21,26,29]

Resistance

Clinically relevant bacterial resistance to rifaximin has not been observed to date. In two clinical trials of patients with travelers' diarrhea, pretreatment rifaximin MICs did not differ from posttreatment MICs for diarrheal pathogens among microbiologic treatment failures.[20,30] In a recently completed and as yet unpublished clinical trial in patients with travelers' diarrhea, MICs of some diarrheal pathogens increased after 3 days of treatment with rifaximin, but a similar increase in MICs among placebo-treated patients makes these data difficult to interpret.[21]

Rifaximin given as a 3-day course of therapy did not appear to induce resistance in enteric flora in a recently published study.[90] Significant increases in antimicrobial-resistant coliform flora were not observed in samples

from either rifaximin-treated subjects or placebo-treated subjects (n=27), and enterococci showed similar susceptibilities before and after a course of rifaximin treatment (n=71). Lack of antibiotic resistance in enteric flora has also been supported in a prevention study, during which rifaximin was administered for 14 days.[88] Rifaximin also does not appear to be associated with cross-resistance to other rifamycins as suggested by the finding that growing *Mycobacterium tuberculosis* in the presence of rifaximin did not result in the growth of rifamycin-resistant bacterial strains in vitro.[91]

These laboratory findings are consistent with observations from clinical practice. Clinically relevant resistance to rifaximin has not been observed during more than 19 years of use of more than 500 million rifaximin tablets for enteric infections. This finding is consistent with the possibility that the circumscribed use of rifaximin (for enteric infections only) results in less pressure for the development of bacterial resistance relative to that observed with systemically available oral antibiotics used for infections affecting multiple body systems. In order to further define the resistance profile of rifaximin, additional studies of bacterial susceptibility are ongoing, and patients treated with rifaximin continue to be monitored for evidence of the emergence of rifaximin-resistant bacteria.

Dosing

The recommended dose of rifaximin for the treatment of travelers' diarrhea is 200 mg three times daily for 3 days. Recommended and FDA-approved doses for other potential rifaximin uses have not been established. Doses that have been assessed in clinical studies and/or employed in clinical practice are shown in Table 4.[88,92]

Conclusions

The preclinical profile of rifaximin—which has broad-spectrum in vitro antibacterial activity against enteric pathogens, gut-localized action, and minimal (<0.4%) systemic absorption—is consistent with that of an antibiotic useful for a range of enteric conditions that involve a pathogenic role of bacteria. The emerging clinical profile of rifaximin also supports its potential utility for multiple enteric conditions. Rifaximin has a tolerability profile comparable to that of placebo and is not known to interact clinically with other medications. The efficacy of rifaximin is well documented for the treatment of infectious diarrhea caused by noninvasive pathogens. A growing body of data supports the efficacy of rifaximin for additional enteric conditions characterized by acute bacterial infection or bacterial colonization. With the exception of the data on rifaximin for infectious diarrhea, however, the currently available data for enteric uses of rifaximin come largely from small, uncontrolled studies. While the results of the uncontrolled studies appear to be promising, the evidence base on the efficacy of rifaximin for potential enteric uses other than infectious diarrhea and hepatic encephalopathy requires supplementation with results of large, controlled studies before conclusions can be drawn. Furthermore, the exact mechanism of action of rifaximin in various enteric conditions has remained speculative. In

Table 3. Adverse Events in Two Placebo-Controlled Studies of Rifaximin for Travelers' Diarrhea[21,26,29]

Adverse Event*	Rifaximin 600 mg/day (n=320), n (%)	Placebo (n=228), n (%)
Flatulence	36 (11.3)	45 (19.7)
Headache	31 (9.7)	21 (9.2)
Abdominal pain	23 (7.2)	23 (10.1)
Rectal tenesmus	23 (7.2)	20 (8.8)
Defecation urgency	19 (5.9)	21 (9.2)
Nausea	17 (5.3)	19 (8.3)
Constipation	12 (3.8)	8 (3.5)
Pyrexia	10 (3.1)	10 (4.4)
Vomiting	7 (2.2)	4 (1.8)

* Adverse events reported in >2% of patients in a group are listed.

Table 4. Dosing of Rifaximin for Several Uses in Clinical Studies and/or Clinical Practice[88,92]

Condition	Dosage
Travelers' diarrhea	200 mg TID for 3 days
Hepatic encephalopathy	• 800 mg/day for 7 days • 400 mg every 8 hours for 5–15 days • 400 mg TID for 14 days each month for 6 months
Intestinal gas	400 mg BID for 7 days
Small-intestinal bacterial overgrowth	400 mg TID for 10 days each month
Active Crohn's disease	400 mg BID
Ulcerative colitis	400 mg BID
Pouchitis	400 mg BID
Diverticular disease	400 mg BID for 7 days each month
Prevention of travelers' diarrhea	200 mg BID or TID for 2 weeks
Irritable bowel syndrome	400 mg TID for 10 days

addition to its antibacterial activity, there has been some evidence that rifaximin may have some anti-inflammatory activity. This anti-inflammatory component has been supported by limited animal data and human tissue sampling.[93,94] Overall, ongoing studies and more experience in clinical practice will help to further define the role of this antibiotic in gastroenterology and hepatology.

Addendum

Several studies presented at the 2005 Annual Scientific Meeting of the American College of Gastroenterology on the efficacy and safety of rifaximin have been published in abstract form. Mark Pimentel and colleagues reported on a randomized, double-blind, placebo-controlled trial demonstrating improvements in symptoms of IBS with rifaximin therapy.[95] In an open-label study by Leonard Baidoo and colleagues, rifaximin was effective in the treatment of mild to moderate active Crohn's disease, whereas a separate study showed rifaximin was effective as a steroid-sparing treatment in the management of inflammatory bowel disease.[96,97]

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